

TITLE: **CHRONIC CONSTIPATION IN ADULTS: CONTEMPORARY PERSPECTIVES AND CLINICAL CHALLENGES. 1: EPIDEMIOLOGY, DIAGNOSIS, CLINICAL ASSOCIATIONS, PATHOPHYSIOLOGY AND INVESTIGATION**

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ABBREVIATIONS:

| | |
|--------|--|
| ACE | antegrade continence enema |
| BET | balloon expulsion test |
| CC | chronic constipation |
| ED | evacuation disorders |
| FC | functional constipation |
| FDD | functional defaecation disorders |
| GI | gastrointestinal |
| GP | general practitioners |
| HR-ARM | high-resolution anorectal manometry |
| IBS-C | irritable bowel syndrome with constipation |
| MRI | magnetic resonance imaging |
| OIC | opioid-induced constipation |
| PRO | patient-reported outcomes |
| RH | rectal hyposensitivity |
| ROM | radio-opaque markers |
| SCFA | short-chain fatty acids |
| STC | slow-transit constipation |
| WMC | wireless motility capsule |

ABSTRACT

BACKGROUND

Chronic constipation is a prevalent disorder that affects patients' quality of life and consumes resources in healthcare systems worldwide. In clinical practice, it is still considered a challenge as clinicians frequently are unsure as to which treatments to use and when. Over a decade ago, a *Neurogastroenterology & Motility* journal supplement devoted to the investigation and management of constipation was published (2009;21(Suppl.2)). This included seven articles, disseminating all themes covered during a preceding two-day meeting held in London, entitled 'Current perspectives in chronic constipation: a scientific and clinical symposium'. In October 2018, the 3rd London Masterclass, entitled 'Contemporary management of constipation' was held, again over two days. All faculty

members were invited to author two new review articles representing a collective synthesis of talks presented and discussions held during this meeting.

PURPOSE

This article represents the first of these reviews, addressing epidemiology, diagnosis, clinical associations, pathophysiology and investigation. Clearly not all aspects of the condition can be covered in adequate detail; hence, there is a focus on particular 'hot topics' and themes that are of contemporary interest. The second review addresses management of chronic constipation, covering behavioural, conservative, medical and surgical therapies.

AUTHORS' CONTRIBUTIONS:

SMS conceived the idea of these review articles. All authors performed the literature search and wrote the manuscript according to the section they were assigned: Introduction: SMS, MC, CK; Epidemiology and diagnosis: MS, JR-T, ED, AF. Clinical associations: ADF, SMS, AF, KN. Pathophysiology: PD, SMS, RB, CK, KW. Investigation: EC, MF, RB, PD, CH, KK. Section Leads were: SMS, MS, ADF, PD and EC. Initially, SMS collated and revised all sections of the manuscript. Section Leads and finally all authors critically revised subsequent versions of the manuscript and approved the final version.

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SMS and EC have received honoraria for teaching for Laborie.

MS has received unrestricted research grants from Danone Nutricia Research, Glycom and Ferring Pharmaceuticals; acted as Consultant/Advisory Board member for Danone Nutricia Research, Nestlé, Menarini, Biocodex, Genetic Analysis AS, Glycom, Arena and Shire; and has been part of the speakers' bureau of Tillotts, Menarini, Kyowa Kirin, Takeda, Shire, Biocodex, Alimentary Health, AlfaSigma, and Falk Foundation.

MB is Consultant for Shire, Norgine, Coloplast, Allergan, FrieslandCampina, HIPPO, Danone and Sensus. RB is a paid speaker for Bayer, NPS medicinewise and Advisory board member for Allergan, Anantara Life Sciences and Atmo Biosciences

ED has received an education grant from Alpro, research funding from the British Dietetic Association, Almond Board of California, International Nut and Dried Fruit Council and Nestec Ltd and has served as a consultant for Puratos.

MF has acted as a paid Consultant and has been paid for speaking and reimbursed for attending symposiums by Medtronic, Reckitt Benckiser and Shire Pharmaceuticals; he has received funding of

research and support of staff by Medtronic, Mui Scientific, Reckitt Benckiser and Nestle International, and has organized educational activities that have been supported by Medtronic, Sandhill Scientific Instruments and Medical Measurement Systems.

CK is a paid Consultant and speaker for Medtronic Inc. He has consulted in the last 3 years for Coloplast, Enetromed and Alimentary Health. He has received funding for research activities from Saluda Medical, Cook Medical, Exero Medical and Takeda. He is a member of committees that benefit from industry sponsorship including the Rome Foundation and The International Anorectal Physiology Working Group.

KN has consulted in the last year for Coloplast.

JMR-T is a Consultant / Advisory Board member for Takeda, Asofarma, Chinoin, Medtronic and Biocodex; he has received research funding from CONACYT, Mexico

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INTRODUCTION

Chronic constipation (CC) remains a clinical challenge, with frequent suboptimal outcomes to a variety of conservative, behavioural, medical and surgical interventions. Over a decade ago, a *Neurogastroenterology and Motility* journal supplement was devoted to the investigation and management of constipation (2009:21 [Suppl. 2]). This included seven articles,¹⁻⁷ disseminating all themes covered during a preceding two-day meeting held in London, entitled 'Current perspectives in chronic constipation: a scientific and clinical symposium'. In October 2018, the 3rd London Masterclass, entitled 'Contemporary management of constipation' was held, again over two days, and again boasting a world-renowned faculty. By way of dissemination, two side-by-side review articles have been produced that represent a collective synthesis of talks presented and discussions held during this meeting. Authorship includes all invited faculty members. These reviews provide not only an update on topics addressed in the previous journal supplement, but also a state-of-the-art overview of the clinical management of constipation. Areas for future research are additionally highlighted. The first of these reviews addresses epidemiology, diagnosis, clinical associations, pathophysiology and investigation. Clearly not all aspects of the condition can be covered in adequate detail; hence, there is a focus on particular 'hot topics' and themes that are of contemporary interest. The second, 'sister' review, addresses management of chronic constipation, encompassing behavioural, conservative, medical and surgical therapies.

EPIDEMIOLOGY AND DIAGNOSIS

Definitions

Constipation is most simplistically defined as unsatisfactory defaecation resulting from infrequent stools, difficult stool passage, or both.⁸ Alternatively, it is a term that embraces a (limited) spectrum of symptoms related to an individuals' personal dissatisfaction with their evacuatory ability.⁴ Symptoms include, though are not restricted to, hard stools, excessive straining, infrequent bowel movements, bloating and abdominal pain,⁹ and if such symptoms last >1 month, constipation is labeled as chronic. CC can be viewed as an umbrella term encompassing all disorders and conditions with long-standing constipation, and can be primary or secondary. Multiple conditions may cause secondary CC, for example, drugs (opioids, calcium channel blockers, NSAIDs), neurological disorders (Parkinson's disease), or metabolic diseases (diabetes).¹⁰ Primary CC (which is the main focus of these reviews) is a condition that is considered to result from dysfunction of colonic regulation of stool

movement, together with uncoordinated or obstructed defaecation, with or without simultaneous abnormal gastrointestinal (GI) sensitivity (hyper- or hyposensitivity).^{11,12}

Epidemiology

When reviewing the epidemiology of CC, it is important to acknowledge that definitions vary across studies (see below). Nevertheless, CC is extremely common amongst adults in the community, with the most recent systematic review and meta-analysis (incorporating 45 population-based studies) showing a global prevalence of 14%.¹⁰ Prevalence increases with age,^{10,13-15} and is almost twice as common in women than men.¹⁰ The meta-analysis also showed a modest increase in prevalence of CC among individuals with the lowest socioeconomic status compared to those with the highest (OR 1.32; 95% CI: 1.11 – 1.57),¹⁰ supporting the results of other previous studies.^{15,16}

Impact of CC on quality of life appears comparable with that of some organic conditions, including chronic obstructive pulmonary disease, diabetes, and depression,¹⁷ and up to 20% of people with CC will ultimately consult a physician.¹⁸ In a recent report on the cost of constipation in the UK, it was estimated that 2 million people suffer from CC, yet up to one-in-five are reluctant to talk to their doctor about their symptoms.¹⁹ The same report also suggested that between 2017 and 2018, almost 200 people were admitted to hospital each day as a result of CC, equating to >160,000 bed days per year, and treatment costs in excess of £160 million, including >£70 million for unplanned admissions and >£90 million for laxatives.¹⁹

Diagnosis and symptom assessment

Constipation is generally considered a symptom-based disorder, with subtypes able to be defined according to the use of diagnostic criteria, such as the Rome IV criteria,²⁰ which are advocated together with a limited number of tests to rule out other diagnoses, as well as for ensuring eligibility for clinical trials.²¹ The Rome IV criteria allows categorisation of disorders of CC into four subtypes: (a) functional constipation (FC), (b) irritable bowel syndrome with constipation (IBS-C), (c) opioid-induced constipation (OIC), and (d) functional defaecation disorders (FDD), the latter including inadequate defaecatory propulsion and dyssynergic defaecation.²⁰⁻²² IBS-C is characterized by a combination of pain and constipation; FC by the presence of constipation symptoms without predominant pain and/or bloating (i.e. criteria for IBS is not met); OIC as new or worsening symptoms of constipation when initiating, changing, or increasing opioid therapy; and FDD as symptoms compatible with IBS-C or FC in combination with objective signs of disturbed rectal evacuation on diagnostic testing.²⁰⁻²²

Conversely, based on presence or absence of detectable physiological abnormalities on diagnostic testing, at least three subtypes of CC (which may overlap) have been described: slow-transit constipation (STC), evacuation disorders (ED, which encompasses structural or functional obstructive phenomena that impede stool expulsion), and normal transit constipation. More widespread use of physiological tests to better define clinical / physiological phenotypes could, in the future, pave the way for improved management of constipation. For example, establishing a diagnosis of a FDD implies the need to use a specific treatment such as biofeedback therapy.

Other available diagnostic tools include the Bristol Stool Form scale, which is a 7-point scale (ranging from separate hard lumps to liquid consistency with no solid pieces) used extensively in clinical practice and research for stool form measurement.²³ This non-expensive and widely available instrument has been shown to be a reliable surrogate marker for whole-gut and colonic transit,²⁴ and has been adapted into several languages and been modified for use in children.

In CC, as in many other chronic diseases where objective findings correlate poorly with reported symptoms, patient-reported outcomes (PRO) are of great importance to evaluate the effectiveness of treatments and disease progression over time. Tools that currently exist to evaluate PRO measures, developed through literature review and input from patient focus groups, include the Patient-Reported Outcomes Measurement Information System (PROMIS) GI symptom item bank,²⁵ which captures symptoms in 8 domains, including constipation,²⁶ and the CC Symptom Severity Measures.²⁷ The Measure Yourself Medical Outcome Profile (MYMOP), a patient-generated outcome measure allowing patients to select the problems that are the most important to them, has also been used in patients with CC.²⁸ Additionally, several specific constipation questionnaires have been developed such as the Patient Assessment of Constipation Symptoms (PAC-SYM), a 12-item self-report instrument divided into abdominal, rectal and stool domains.²⁹ PAC-SYM has been used in several clinical trials and is considered a reliable and valid tool in adult patients. Other validated scores, such as the Cleveland Clinic constipation score (CCCS)³⁰ and the Knowles-Eccersley-Scott-Symptom (KESS) score³¹ have been developed to identify subtypes of CC more from a clinical than a mechanistic perspective.

Perceptions of constipation

Despite the existence of formal diagnostic criteria for constipation disorders (e.g. Rome criteria),^{20,32} evidence suggests that patients and clinicians often diagnose CC more pragmatically, based on the assessment of symptoms *they* consider important for a diagnosis. Indeed, a study showed that general

practitioners (GPs) did not typically use the Rome criteria in clinical practice, and focused only on stool frequency and consistency to diagnose CC.³³ Similarly, a recent cross-sectional study in 2,557 members of the general population, 411 general practitioners and 365 specialist gastroenterology doctors demonstrated that only 46%-58% of the general population and 39%-73% of clinicians correctly identified FC when provided with case studies of patients meeting the Rome IV criteria for functional constipation.³⁴ The same study also highlighted differences in symptoms perceived to be important for a diagnosis of constipation; for example, infrequent bowel movements was most frequently reported as important for a diagnosis by specialist gastroenterologists and colorectal surgeons, compared to less than a third of constipated and non-constipated members of the general population.³⁴ Moreover, this and other studies indicate that symptoms outside of the Rome criteria, such as pain during defaecation and spending a long time on the toilet without passing a stool, are used by the general population to define CC, confirming differences in perceptions of CC between the general population and clinicians.³⁴⁻³⁶ Such differences may impact patients' clinical care, including diagnosis and treatment, reinforcing the need to also use PRO measures in clinical practice to assess patients' individual needs.

Disorders with chronic constipation: are they distinct entities?

Accumulating clinical and mechanistic evidence suggests that the different disorders of CC exist on a spectrum rather than being distinct entities, as highlighted in the most recent version of the Rome diagnostic criteria for functional bowel disorders.^{20,37} It is further acknowledged that it is sometimes difficult to distinguish one from another, as overlap commonly exists, and that transition from one functional bowel disorder or from one predominant symptom to another is frequently seen. Specifically, considerable overlap between IBS-C and FC exists when mutual exclusivity is suspended,³⁸⁻⁴¹ and transition from FC and IBS-C, and *vice versa*, is common.^{41,42} Also, when reviewing studies assessing the pathophysiology of IBS-C and FC, a considerable overlap can be seen, even though certain abnormalities, e.g. visceral hypersensitivity seems to be more prominent in IBS, and others, e.g. abnormal colonic motility, seem to be more related to FC (Figure 1).⁴³

Paediatric chronic constipation and transition to adult medical care

There are similarities between paediatric and adult constipation (e.g. hard stools, with painful and infrequent bowel movements, often accompanied by symptoms of bloating and abdominal pain).⁴⁴ However, in contrast to adults, children more often present with coexistent faecal incontinence, caused by overflow of soft stools passing around a rectal faecal mass. Moreover, children rarely complain of the sense of incomplete evacuation or obstruction, or the requirement of manual

manoeuvres to defaecate. Further, differences in response to conventional strategies such as biofeedback therapy and pharmacotherapy, and different surgical outcomes following neuromodulation and antegrade continence enema (ACE) surgery, suggest that childhood functional constipation may be a different entity from adult functional constipation.⁴⁴ However, transition to adult care is of fundamental clinical importance, since a long-term follow-up study (median follow-up of 11 years) showed that 25% of children still experience symptoms of constipation as adults, and that many continue to have severe symptoms.⁴⁵ A recent UK guideline on transition of adolescent and young persons with chronic GI conditions from paediatric to adult care recommends the use of structured transition programmes to improve GI disease control, which better ensures adherence to medications, clinic attendance and clinical outcomes.⁴⁶ In addition, such programmes may improve psychological outcome and health-related quality of life, and may reduce adverse outcomes such as hospitalisation and surgery. Currently, however, outpatient transition clinics exist for patients with inflammatory bowel disease, but are lacking for patients with functional gastrointestinal disorders, including constipation.⁴⁷

Areas for future research

1. More information about the costs of constipation to health services, and society as a whole, globally.
2. Further exploration of means to facilitate the transition from adolescents with CC to presentation in adult gastroenterology care.
3. Better understanding of risk factors for constipation in the community.
4. Defining relevance of results from (patho)physiological testing for symptoms and outcome of treatment in patients suffering from constipation with and without other accompanying GI symptoms.
5. Can more detailed assessment of the symptom profile (standardised questionnaires, bowel habit diaries etc.) predict physiological abnormalities among patients with constipation symptoms?
6. Are there specific and clinically relevant phenotypic subgroups among subjects presenting with constipation, and can these subgroups can be reliably (and cost-effectively) identified in the clinical setting.
7. Integration of doctors' and patients' perceptions of a constipation diagnosis into the formal diagnostic criteria for constipation; this will also be informed by a better understanding of PRO measures.

CLINICAL ASSOCIATIONS

A number of clinical conditions are associated with CC, and a comprehensive review of all is beyond the scope of this review. Nevertheless, several conditions are of notable contemporary interest, as the knowledge base regarding their association with CC accumulates. These include: (1) faecal incontinence (FI), whose coexistence with CC has been grossly underappreciated in adult populations; (2), connective tissue disorders, especially hypermobile Ehlers-Danlos syndrome (hEDS); (3) post-surgical intervention, most notably following surgery for colorectal cancer; (4) as a sequelae to opioid therapy, given the current opioid epidemic in Western society, and (5) comorbid mood disorders.

Faecal incontinence

FI affects 8 – 12% of the adult population⁴⁸⁻⁵⁰ and can have a devastating negative impact on quality of life.⁵¹ Though long-considered to predominantly affect females secondary to obstetric-related anorectal injury, recent epidemiological studies show prevalence is equivalent between genders,^{48,49} indicating that pathoetiological factors other than traumatic childbirth *must* play a role.^{52,53} Loose stools and faecal urgency are key, well recognised risk factors for FI,^{48,54,55} but in both paediatric^{56,57} and geriatric populations,^{58,59} a major underlying cause for FI (in >80% of patients) is considered to be constipation.⁶⁰ Unfortunately, this relationship has been grossly neglected in the general adult population. However, recent data indicate that in a sizeable proportion of patients (up to 69%), significant symptoms of FI and CC coexist;⁶¹⁻⁶⁵ with recognition of this frequently overlooked by the referring clinician.⁶⁵

Pathophysiology of concurrent FI and constipation is undoubtedly multifactorial, though coexistence suggests some commonality of underlying mechanisms (see Figure 2).^{60,66} Over 30 years ago, Swash *et al.* proposed a unifying hypothesis for pelvic floor disorders (including constipation) and FI which still holds merit today, where obstetric injury (females) or constipation (males and females), characterised by chronic straining at stool, lead to denervation of the pelvic floor and anal sphincter musculature and ultimately to FI, with consequent pelvic floor descent (and possibly prolapse) resulting in progression of the neurogenic lesion.⁶⁷ They have recently revised this hypothesis to include traction injury to pelvic floor suspensory ligaments, with laxity leading to inactivation of anorectal muscle force vectors during defaecation and worsening of the (underlying) evacuation disorder.⁶⁸ Other important pathophysiological mechanisms include ‘overflow’ secondary to faecal impaction (e.g. with a megarectum or severe evacuation disorder, often allied to hyposensitivity),^{69,70} or where FI results

from incomplete rectal evacuation whether by structural^{65,71,72} or functional cause,⁷³ often in the presence of abnormal anal sphincter function / structure.⁶⁵

Acknowledgment of coexistent FI and constipation has major implications regarding management. If FI is indeed secondary to underlying constipation, then intervention directed to improving constipation symptoms and efficacy of evacuation should be considered first-line treatments. Several studies have demonstrated significant improvements or resolution of symptoms of FI when causes of evacuatory dysfunction have been addressed (e.g. after surgical repair of rectocele and / or intussusception,⁷⁴⁻⁷⁶ and following colorectal irrigation).⁷⁷

Connective tissue disorders

Constipation is present in up to 50% of patients with connective tissue disorders, be they inflammatory (e.g. systemic sclerosis: SSc) or non-inflammatory (e.g. hEDS),^{78,79} and this is more common in patients who have systemic involvement.^{78,80} GI symptoms can precede the systemic manifestations and therefore the diagnosis of a connective tissue disorder.

SSc is characterized by autoimmune-mediated neuropathy, myopathy and fibrosis within the GI tract. Constipation is most common in those patients with upper GI involvement, and can be due to slow gastrointestinal transit⁸¹ or anorectal dysfunction.⁸² In severe cases, gut dysmotility caused by the underlying pathology can lead to chronic intestinal pseudo-obstruction. Prucalopride, stimulant laxatives and, in refractory cases, neostigmine can be effective for slow-transit constipation in SSc.⁸³ Fibre worsens bloating and should be avoided.⁸⁴ In terms of anorectal dysfunction, anal hypotension, a reduced or undetectable recto-anal inhibitory reflex⁸⁵ and increased rectal sensitivity to balloon distension⁸⁶ are typically seen on diagnostic testing. Over time, symptoms of diarrhoea and FI can develop due to the development of small intestinal bacterial overgrowth and atrophy of the internal anal sphincter, respectively, both consequences of the underlying connective tissue disorder.⁸⁷

Ehlers Danlos Syndrome (EDS) is a non-inflammatory connective tissue disorder characterised by joint hypermobility, tissue fragility and musculoskeletal symptoms. hEDS is the most common subtype of EDS and is the only one in which the aetiology and genetic marker have not been identified. The prevalence of constipation is higher in hEDS than in other EDS subtypes.⁸⁸ Constipation can be present from early life,⁸⁹ with progression to an alternating bowel habit in some.⁹⁰ Symptoms of an ED are very common,⁹¹ and there is a high prevalence of rectal hyposensitivity,⁸⁹ dyssynergic defaecation and rectal morphological abnormalities.⁶² Colonic transit may be delayed,⁸⁸ though this may be secondary

to a coexistent ED. Treatment is holistic, involving lifestyle advice, opiate withdrawal, and laxatives/irrigation therapy as appropriate for the underlying pathophysiology. Surgery for constipation in SSc and hEDS is relatively contraindicated because of the risk of anaesthetic complications, wound problems and postoperative ileus.^{92,93}

Following colorectal surgery

Colorectal cancer is the third most common cancer, with 1.8 million new cases diagnosed worldwide in 2018;⁹⁴ the majority of these will be treated surgically, and 50-60% of patients now survive long-term (greater than 10 years). New symptoms of bowel dysfunction are common post-operatively. For example, symptoms such as FI, faecal urgency, constipation, fragmentation of stool, and frequent bowel movements constitute a major problem following low anterior resection (LAR),⁹⁵ which is performed in up to 80% of patients undergoing surgery for rectal cancer.⁹⁶ These symptoms are collectively referred to as the low anterior resection syndrome (LARS), with 40-50% of patients having long-term LARS to an extent that it significantly impairs their quality of life.^{97,98} In patients undergoing surgery for colon cancer, a recent study showed that 21% suffered from LARS-like symptoms post-operatively;⁹⁹ this is a similar proportion to the number of patients reporting a sense of incomplete rectal emptying after sigmoid colectomy.¹⁰⁰

The reasons behind the poor functional results after both rectal and colon cancer surgery have yet to be established, though tumour height and location, gender and preoperative radiotherapy are important factors. Pathophysiology is considered to be multifactorial,⁹⁶ with loss of neurological continuity, compromised neorectal sensory-motor function allied to surgical excision of the rectal reservoir,^{96,101} anal sphincter dysfunction^{102,103} and increased colonic motility^{104,105} considered primary mechanisms. Management following bowel cancer surgery is empirical and symptom-based, using existing therapies for FI, urgency, evacuatory difficulties etc.⁹⁶

Opioid-induced constipation

Opioids are associated with substantial adverse effects, including those arising from the GI tract such as nausea, vomiting and constipation; collectively referred to as opioid-induced bowel dysfunction (OIBD). The most prevalent form of OIBD is opioid-induced constipation (OIC) which occurs in up to 87% of patients with pain related to cancer, although rates are approximately 50% in those with non-cancer pain.¹⁰⁶⁻¹⁰⁸ OIC is associated with reduced work productivity and quality of life, yet remains under diagnosed.¹⁰⁹⁻¹¹¹ The Rome IV criteria define OIC as a change in bowel habit or defaecatory patterns, in comparison to normal following initiation, alteration or an escalation in opioid therapy,

see Table 1.²⁰ Two recent cross-sectional studies comparing symptoms and results of diagnostic testing in constipated patients either currently taking or not taking opioids have shown that opioid use is associated with increased symptom severity, diminution in quality of life, and a greater incidence of rectal hyposensitivity, functional ED / dyssynergic defaecation, and delayed whole-gut transit.^{112,113}

Mood disorders

The role of psychological factors has been extensively evaluated in the context of functional gastrointestinal disorders (FGIDs). Traumatic events, childhood physical and sexual abuse are independently associated with a higher incidence of FGIDs.¹¹⁴ The personality trait of neuroticism is particularly associated with constipation.¹¹⁵ In addition, it is well established that FGIDs are linked with an increased prevalence of concomitant disorders of anxiety and depression although there is controversy as to the directionality of this association. In a large prospective study, Koloski *et al.* demonstrated that higher levels of anxiety, but not depression, conferred an approximate 10% increase in risk of developing a FGID over the subsequent 12 years.¹¹⁶ In a further study, Jones *et al.* reported that the median time period between diagnosis of an affective disorder and FGID was 3.5 years, compared to a median time period of 1.8 years between a FGID and a diagnosis of an affective disorder.¹¹⁷ However, this study failed to demonstrate such an association for constipation *per se*.

Areas for future research

1. Further evaluation of the cause and effect relationship between constipation and faecal incontinence.
2. To systematically characterise pathophysiology underlying constipation in hEDS and develop specific evidence-based treatments.
3. Evaluation of the reasons why rates of OIC are higher in cancer pain vs. non cancer pain.
4. Though early-life events may be an important factor in the pathogenesis of paediatric constipation, their impact on chronic (?lifelong) constipation in adults is unknown, and warrants investigation.
5. Prospective evaluation of the potential causal relationship of individual mood disorders on slowing colonic motility and causing constipation.
6. The effect of successful treatment of mood disorders on colonic motility.

PATHOPHYSIOLOGY (see Figure 3)

Colonic dysmotility

Abnormalities of both colonic transit and contractility are commonly associated with CC. Tests of gut transit (see below) can diagnose a patient with normal or slow transit constipation; the latter is typically characterised by delayed movement of intraluminal content through the ascending and transverse colon.⁹ In patients found to have delayed transit localised to the distal colon, this may be associated with an ED, though data are conflicting as to whether the transit delay is secondary to the ED or *vice versa*, or indeed they are independent.^{9,118} In patients with STC, abnormal colonic contractility has been characterised to an extent, and in comparison to healthy adults, these patients have a reduction in: 1) number of high-amplitude propagating contractions, a propulsive motor pattern associated with mass movement and defaecation;¹¹⁹⁻¹²² 2) the postprandial cyclic propagating motor pattern, which is hypothesized to help mix and control the flow of content (see Figure 4);¹²³ and 3) pre- and post-prandial colonic pressurizations, synchronous pressure waves recorded across all recording channels, hypothesized to be associated with gas transport.¹²² In constipated patients with normal transit constipation or a distal colonic delay, abnormalities of motor activity remain poorly described.

Upper gut dysmotility

Oesophageal, gastric and small bowel motility abnormalities have also been described in patients with CC. A recent study showed that in patients reporting overlapping symptoms of dyspepsia and constipation, those diagnosed with STC were significantly more likely to have a coexistent delay in gastric emptying when compared to those with normal transit constipation.¹²⁴ In another study of 91 STC patients, 31 were diagnosed with delayed gastric emptying and 9 had delayed small bowel transit.¹²⁵ Manometry studies have additionally shown oesophageal and small bowel contractile dysfunction in constipated patients with normal or delayed colonic transit.¹²⁶⁻¹²⁸ Whether such findings represent reflex inhibition of proximal GI motility or a shared primary disorder of the enteric nervous system is unknown.

Evacuation disorders

Although the medical literature is littered with synonyms (e.g. defaecation disorder, outlet obstruction, obstructive defaecation disorder, obstructed defaecation etc.), 'evacuation disorder' (ED) is now the accepted term to describe the clinical and / or laboratory features relating to an individual's inability to satisfactorily expel stool.^{1,4,9,12} Clinically, the majority of patients with CC complain of

symptoms suggestive of an ED, with straining the most commonly reported individual symptom.^{34,130} Indeed 4 of the 6 diagnostic symptoms comprising the Rome IV criteria for FC are compatible with an ED.²⁰

The primary pathophysiological mechanisms responsible for EDs are considered to be structural or functional obstructive phenomena that impede the expulsion of stool, though these may overlap.¹³¹ Structural features providing a mechanical barrier to evacuation include high-grade rectal intussusception and enterocele, whereas misdirected (into 'trapping' rectocoeles, which are usually large, >4 cm)¹³¹ or dissipated force vectors recruited during straining (with descending perineum syndrome and full-thickness rectal prolapse) may also impede evacuatory ability.^{4,132} Approximately 7% of patients with symptoms of ED will have a megarectum, allied to diminished or absence of rectal filling sensation.^{12,131,132} Structural phenomena often occur in combination as part of a more global pelvic floor disorder.^{131,133,134}

Functional EDs (or FDDs), first described in the mid 1980's,¹³⁵⁻¹³⁷ are characterised by recto-anal incoordination, manifest as paradoxical involuntary contraction or failure of relaxation of the anal sphincter and pelvic floor musculature (principally puborectalis), and / or inadequate abdomino-rectal propulsive forces.^{4,32,132} Functional EDs are often associated with blunted rectal sensation (hyposensitivity),^{12,32,138} and also anal hypertonia in a small proportion.^{139,140}

On testing, >80% of chronically constipated patients may be diagnosed with pathophysiological features compatible with an ED.^{131,141} However, both diagnostic yield and observable cause (structural vs. functional obstruction, or both) are heavily dependent on both the technology used for data acquisition and the approach to data analysis applied.^{131,142-144}

Sensory dysfunction

Normal defaecation requires a conscious sensation of rectal filling and urge to defaecate. It is therefore not surprising that impaired or reduced rectal sensation (rectal hyposensitivity: RH; practically defined as a diminished perception to rectal mechanical distension, manifest as elevated sensory thresholds), is associated with disordered defaecation. Observational studies indicate RH is found in up to 60% of constipated patients, 10% of patients with faecal incontinence and 27% of individuals with symptoms of both.^{70,145} In the largest study published to date (2,876 patients), 25% of patients were found to have RH, with a linear relationship existing between the number of elevated sensory thresholds to rectal distension and constipation severity.¹⁴⁶

The aetiology of RH is uncertain, but a number of mechanisms have been proposed. In some patients, in whom there is documented disruption of the afferent pathway (e.g. due to pelvic nerve damage or spinal cord injury),^{147,148} there is a clear cause-effect relationship with development of RH. For example, 78% of patients with complete spinal cord injury and hindgut dysfunction, and 43% of individuals with incomplete lesions have RH.^{149,150} RH is also an important mechanism in patients with constipation following stroke¹⁵¹ and associated with multiple sclerosis.¹⁵² In others, behavioural inattention to defaecation (i.e. voluntary withdrawal of attention from rectal sensations and/or habitual suppression of the desire to defaecate) is a likely factor.¹⁵³ However, in the majority of patients with chronic constipation, it remains unclear whether RH is a primary pathology leading to increasing severity of symptoms, whether chronic constipation itself results in the development of RH, or if indeed RH is an epiphenomenon.^{113,154}

With regard to pathophysiology of RH in CC, this is considered to be either due to dysfunction of the afferent pathway ('primary' RH), as a result of altered rectal wall biomechanics (i.e. increased capacity or hypercompliance ('secondary' RH: see Figure 5), or both.¹⁵⁵ Symptomatically, RH is associated with "no urge constipation"^{156,157} and is more common in individuals meeting the Rome IV criteria for FC (60%) rather than IBS-C (2%).¹⁴⁵ RH appears to be linked primarily to ED,¹³⁸ and particularly with "functional" rather than a mechanical (anatomical) obstruction to defaecation.^{12,32,70,138,158}

RH impacts CC via two key mechanisms: 1) through its association with functional ED either directly, due to co-incident/corresponding efferent dysfunction (i.e. concurrent reduced rectal contractility),^{154,159} or indirectly via the development of large, hard and difficult to evacuate stools due to faecal retention and desiccation secondary to reduced awareness; and 2) due to colonic transit delay via inhibitory feedback loops triggered by chronic rectal distension.^{160,161}

Genetic factors and enteric neuropathies

The question of whether CC (especially STC) occurs as a result of an enteric neuropathy, and whether this might be genetically determined has prevailed in the scientific literature since the 1960s, being mainly predicated on clinical observations of early-onset symptomatology and positive family history.¹⁶²⁻¹⁶⁴ However scrutiny of this literature shows little or no evidence of Mendelian inheritance, unaffected monozygotic twins, and where studied, similar rates of family history in community controls.¹⁶² The hypothesis is also attractive because of the known genetic causation of certain bona fide enteric neuropathies, notably Hirschsprung disease. The finding of kindreds (some with a

Mendelian disposition) where Hirschsprung and STC co-segregate^{164,165} has prompted candidate gene approaches such as for mutations of the *RET* gene in patients with STC. These have proved unrewarding.¹⁶⁶ It seems likely that a search for a genetic aetiology will be consigned to genome-wide association studies, which have determined weak susceptibility factors in IBS-C,¹⁶⁷ or to recognition that epigenetic factors may be more important.

The question of whether an enteric neuropathy underpins the transit disturbance in STC is mired by issues of defining neuropathy histologically. This issue is part technical (right specimen, adequate sampling, right preparation, right staining etc.) and part interpretive, the latter being especially problematic when neuronal quantification is attempted.¹⁶⁸ Thus early reports using sledge microtome thick sections and silver staining^{169,170} should be discounted in favour of modern approaches.¹⁷¹ With the exception of a single high quality study from Germany,¹⁷² it is fair to summarise that there is no strong evidence for neuropathy based either on cytoskeletal evidence of cell degeneration or of quantifiable neuronal loss (based on 12 studies from the modern era).¹⁷¹

Dysbiosis

Numerous case-control studies have now compared the gastrointestinal microbiome between CC, IBS-C and healthy controls. In general, studies in adults report lower bifidobacteria and bacteroides in constipation, with some also reporting lower lactobacilli, although these findings are not consistently demonstrated in paediatric patients.¹⁷³

One noteworthy study using 16S ribosomal RNA gene sequencing to measure both stool and mucosal microbiome reported marked differences in mucosal microbiome at both the family level (lower proportions of Comamonadaceae and Odoribacteraceae, higher Flavobacteriaceae and Caulobacteraceae) and genus level (higher Flavobacterium and Mycoplana, lower Delftia and Odoribacter).¹⁷⁴ Multivariate analysis (adjusting for age, body mass index, diet) showed that although stool microbiome composition was significantly associated with colonic transit time, it was mucosal microbiome composition that was significantly associated with constipation even after adjusting for transit time.¹⁷⁴

In terms of microbiome metabolites, there is inconsistent evidence regarding differences in short-chain fatty acids (SCFA) between constipated and healthy subjects; one challenge being that slower colonic transit time can reduce stool SCFA by increasing their colonic absorption rather than decreasing their production.¹⁷⁵ Meanwhile, positive methane breath tests to a carbohydrate challenge

have been shown in some (but not all)¹⁷⁶ studies to be more common in people with STC than both normal transit constipation and healthy controls,^{176,178} and also in IBS-C compared to diarrhoea-predominant IBS.¹⁷⁹ Nevertheless, there appears to be no correlation between methane production and constipation symptom severity.¹⁸⁰ Furthermore, observational case-control studies that have identified alterations in the microbiome and their metabolites are unable to establish whether these differences are a cause or merely as a consequence of constipation.

A direct causal relationship of the microbiome on gut motility has been demonstrated in mice, where the prolonged whole gut transit time in germ-free mice (457 min) was shown to be shortened in germ-free mice colonized with human microbiome (285 min), and this was related to greater colonic contractility in the humanised mice.¹⁸¹ Furthermore, manipulation of murine whole gut transit time led to profound changes in gut microbiome. Polyethylene glycol induced more rapid transit time and resulted in lower abundance of Peptococcaceae, Eubacteriaceae, and Anaeroplasmataceae and higher Bacteroidaceae and Peptostreptococcaceae, whilst loperamide induced slower transit time and resulted in a higher Firmicutes:Bacteroidetes ratio and lower Lachnospiraceae.¹⁸¹ These murine experiments identify a role for the gut microbiome in influencing gut transit and imply that the altered microbiome described in human case-control studies may, in part at least, be a factor involved in the pathogenesis of constipation.

Areas for future research

1. While motor and transit abnormalities have been recorded through various regions of the gut in patients with constipation, we still have a poor understanding of i) how motor patterns relate to movement of content; and ii) how motor patterns in one region of the gut relate to motor patterns in adjacent regions. Are abnormal motor pattern in the small bowel part of a general pan-enteric disorder or secondary to reflex inhibition as a consequence of delayed transit through the colon?
2. There is recognised overlap between ED and delayed whole gut / colonic transit. The question as to which is primary and which is secondary (or do they coexist?) remains an area of debate and warrants further research.
3. While the presence of RH can negatively impact on treatment outcomes,¹⁸² RH itself has been proposed as a therapeutic target.¹⁸³ Specific sensory bowel retraining therapy has been shown to improve sensory dysfunction (in up to 92% of individuals) with corresponding improvement in symptoms.^{184,185} However, further high quality controlled studies are required and this is an orphan area for drug development.

4. Further studies are also required to define the overall clinical impact of RH in hindgut dysfunction.
5. An understanding of dysbiosis and its effects on nerves either directly or via longer term epigenetic changes in nerves or glia are needed. Fundamental studies are required to understand how enteric neurons survive, if they turnover and whether they do so from glia or neuronal progenitors.

FUNCTIONAL DIAGNOSTIC INVESTIGATIONS

Advanced diagnostic studies of colonic, rectal and anal function are recommended in patients in whom organic disease has been excluded, who have failed first-line conservative therapies, such as optimisation of stool consistency, bowel habit training and lifestyle advice, and who are also refractory to standard pharmacological treatments.^{186,187} The aim of investigation is to provide clinically relevant measurements that explain the cause of symptoms, identify pathology, and guide effective management. No one technique provides a complete description of defaecation; instead, a combination of tests to evaluate structure, motor and sensory function are generally employed.¹²⁹ Unfortunately, inconsistency in approach exists due to conflicting data on the usefulness of these investigations for decision making, variability in local expertise and resource availability. Below is a description of the use, merits and pitfalls of the most commonly employed techniques (see also Table 2).

Tests of gut transit

In patients with CC, tests of transit may be useful in those who report infrequent defaecation. Although traditional radiological methods (radio-opaque markers [ROM] and scintigraphy) tend to focus on quantification of colonic transit, it is now appreciated that dysmotility is not necessarily restricted to the colon (see above) and therefore newer techniques (wireless motility capsule [WMC] and 3D-Transit method) have the ability to assess pan-enteric function.

ROM testing is considered a screening investigation, and is indicated to differentiate between normal and slow whole-gut transit (often reported as 'colonic' transit time, though this is overestimated, as oro-caecal transit is a mean of 8 hours, even in healthy volunteers).¹⁸⁸ The test is inexpensive and easy to perform, and results correlate with stool form; for example, prolonged transit time is associated with hard stools. Several ROM protocols exist; the simplest involves the intake of markers (typically 20 – 50) at a single time-point, followed by a single abdominal X-ray, usually after 120 h;¹⁸⁹ transit is defined as abnormal if >20% of markers are retained at the time of the X-ray (see Figure 6A).¹⁸⁹ This

provides a surrogate of disease severity that is more accurate than subjective assessment of faecal loading on an X-ray film.¹⁹⁰ Alternatively, markers can be taken on consecutive days, enabling assessment of mathematically-derived whole-gut and regional colonic transit times.^{191,192} However, such calculations are based on the assumption that transit time is a continuous variable; recent studies employing other methods (e.g. WMC and 3D-Transit) have demonstrated, in sizeable healthy volunteer studies, that whole-gut transit times are, in fact, clustered at intervals separated by approximately 24 hours.^{188,193}

Scintigraphy is recognised as the ‘gold-standard’ method for assessing colonic transit time, but availability is limited to a few specialist centres.¹⁹⁴ The technique involves following the progress of a radioisotopic chemical (e.g. ¹¹¹Indium) through the GI tract using a gamma camera and taking serial scintigrams.¹⁹⁵ Diagnosis of delayed colonic transit is determined by position of the geometric centre of the isotope mass at given time points. The test can be extended to include assessment of gastric and small bowel transit also.¹⁹⁶

The WMC (SmartPill, Medtronic, USA) and 3D-Transit system (Motilis Media, SA, Lausanne, Switzerland) are ingestible capsule devices. The WMC is commercially available, and measures pH, temperature and intraluminal pressure as it traverses the gut.^{192,197} Total and regional gastrointestinal transit times are determined from stereotypical changes in pH and temperature (see Figure 6B); however, accurate information on segmental colonic transit times cannot be determined. The test has been validated against ROM and scintigraphy.^{197,198} At present, the 3D-Transit system is an experimental investigation only; through tracking of the location and orientation of ingested electromagnetic capsules, it offers the potential to assess total and regional GI transit times, segmental colonic transit times,¹⁹³ and also colorectal motility patterns.¹⁹⁹

Tests of colonic motility

Colonic manometry can be employed for advanced investigation of colonic motility in highly selected patients.¹⁸⁷ It is generally used to determine the presence or absence of colonic motor patterns in response to physiological and chemical stimuli.²⁰⁰ Several protocols exist, but most commonly, after bowel preparation, a catheter incorporating >20 recording sensors, spaced between 10 – 30 mm apart, is placed into the colon with the aid of a colonoscope.²⁰¹ With the subject awake, data is collated over a 1-2 hour period before and after a high calorie meal. This can then be followed by assessing the colonic response to intraluminal infusion of a stimulant laxative (e.g. Bisacodyl).²⁰² Though information on colonic motility patterns and propagating sequences can be acquired, standardisation of the

technique is in its infancy.²⁰² Catheter types, the number of sensors and the spacing between them, types of meals and the analysis and interpretation of results all differ amongst different centres. Further, due to a limited number of studies in healthy subjects, a clear definition of 'normal' colonic motility is lacking. Nevertheless, high-resolution techniques are revealing motor patterns that were previously undetected using conventional technology.²⁰³

The use of magnetic resonance imaging (MRI) to investigate colonic motility is experimental at present, but allows for the direct visualisation of either colon wall²⁰⁴ or the contents of the lumen.²⁰⁵ Using cine MRI and post-processing techniques,²⁰⁶ it is possible to track colon wall motion prior to and following a laxative challenge²⁰⁷ and to visualise how the luminal contents are moving, using spatio-temporal maps of luminal contraction and dilation. Further, assessment of colonic wall motion can be combined with other MRI measures e.g. transit²⁰⁸ and volume,²⁰⁹ to provide an objective view of the colon, both in terms of anatomy and function.

Tests of evacuation

Tests of evacuation are useful in patients with CC, especially those who report symptoms of ED. The balloon expulsion test (BET) and defaecography are direct measures of the ability to expel rectal contents, whereas high-resolution anorectal manometry (HR-ARM) is an indirect test of evacuation, which, in this setting, provides information primarily on recto-anal co-ordination.

The BET is a widely used, simple, inexpensive, office-based test that is easy to interpret. It is used as a screening investigation of evacuation, and provides quantitative information on the time taken to expel a 50 ml water-filled rectal balloon. The upper limit of normality is generally accepted to be between 1-3 minutes, and expulsion times that exceed this suggest impaired evacuation.^{210,211} Though there is good test reproducibility, and results help predict response to biofeedback therapies,²¹² BET provides information only on the ability and time taken to evacuate, not on the reason for failure (e.g. obstructive anatomy or dyssynergia).¹²⁹ Further, the use of a small balloon is criticised as a poor analogue for stool which may not generate a normal urge to defaecate.²¹¹

Defaecography is the only direct test of evacuation which provides detail of anatomical variants which may obstruct rectal emptying, as well as identifying 'functional' obstructive causes.¹³¹ It may be performed using fluoroscopy or MRI,¹³¹ with a contrast paste inserted into the rectum to act as a stool surrogate. The patient is then asked to evacuate this paste while representative images are acquired. Physical barriers to expulsion (e.g. rectocele, enterocele, intussusception) can be described, as well

as ability to co-ordinate the pelvic floor musculature during evacuatory manoeuvres.^{131,213} MRI in particular provides excellent assessment of all pelvic floor compartments.²¹⁴ Defaecography, when performed in the sitting position with a native urge to defaecate, is considered the test of evacuation with the most construct validity.¹²⁹ Nevertheless, there is significant variability in measures used for reporting of results which limits transferability of data.¹³¹ Additionally there is some overlap of findings between symptomatic and control subjects, especially in parous women.²¹⁵ MRI defaecography is criticised for generally being performed in the supine position, as open-magnet scanners, that allow imaging in the upright position, are available only in specialised centers.²¹⁶ Barium defaecography does not image soft tissues and requires the use of ionising radiation. Pelvic floor ultrasound may be considered an alternative indirect screening test, in that it allows visualisation of prolapse of pelvic floor structures, though the consequences of any identified prolapse on evacuatory function are unclear from this investigation alone.^{217,218}

HR-ARM is widely available and easy to perform. As part of a standardised protocol recommended by the International Anorectal Physiology Working Group,²¹⁹ the 'push' manoeuvre provides information on recto-anal co-ordination through simultaneous measurement of both anal and rectal pressures. Data are interpreted both quantitatively and qualitatively, with the aid of colour contour plots.²¹⁹ Together with an abnormal direct test of evacuation (BET of defaecography), abnormal patterns of recto-anal co-ordination, manifest as poor rectal propulsion and/or anal dyssynergia, are used to diagnose dyssynergic defaecation,³² recognised in the new international 'London' Classification as minor disorders of anorectal function.²¹⁹ HR-ARM is recommended to be performed in the left lateral position with an empty rectum¹²⁹, but has poor content validity under such circumstance; studies in the upright, seated position are feasible and evidence is accumulating to suggest that this may improve test performance.²²⁰⁻²²² However, interpretation can be difficult as there is a wide overlap of findings between symptomatic and control subjects. In particular, blinded diagnostic accuracy studies suggest that specificity of previously well accepted manometric patterns of dyssynergia may be as low as 13%.²²³ This contrasts with a high level of diagnostic agreement between qualitative assessment of HR-ARM data and MRI defaecography for dyssynergic defaecation,²²⁴ highlighting the requirement for results of indirect and direct tests of evacuation to be consistent.

One emerging tool is Fecobionics,²²⁵ a 10 cm long simulated stool probe containing various sensors assessing pressure, orientation, and bending during evacuation. It combines a direct assessment of evacuation time (validated against BET) with physiological measurements detailing recto-anal

coordination and rectal sensation. Novel evacuation patterns are also described using preload-afterload pressure analysis.²²⁵

Tests of rectal sensation

Tests of rectal sensation are an essential part of the comprehensive diagnostic assessment of individuals with CC, as intact visceral sensory pathways are essential to normal bowel function. Distension of the rectum using an intrarectal balloon²²⁶ is the most widely employed method for quantifying rectal sensitivity, and is often performed as part of an anorectal manometry protocol. The London Classification²¹⁹ recommends documentation of three sensory thresholds using a ramp distension or incremental phasic distension protocol: first constant sensation volume, defaecatory desire volume and the maximum tolerated volume. Elevated thresholds indicate rectal hyposensitivity, diminished thresholds indicate rectal hypersensitivity.²¹⁹ Balloon distension is economical, technically easy and accessible. However, it is confounded not only by inflation protocols²²⁷ but also the elastic recoil properties of the balloon itself, and thus, in the presence of abnormal sensory thresholds, the test cannot distinguish between afferent nerve dysfunction, hyper/hypo-compliance or dilation of the rectum.²²⁸ Accordingly, balloon distension should be considered a screening test of visceral sensation.

The recognised gold-standard for determining visceral sensation to distension is the electromechanical barostat,^{226,229} a computer-controlled piston connected to a distensible bag with a volume larger than the viscus being examined (i.e. the bag is effectively infinitely compliant). The bag is inflated and deflated automatically to maintain a constant pressure within the rectum while volume is continuously recorded.²³⁰ Barostat recordings are not affected by the recoil properties of the bag, hence permitting the determination of rectal wall bio-elastic properties (e.g. compliance and capacity: see Figure 5).^{226,228,231,232} The test is reproducible across laboratories and between patients.^{229,233} However, restricted availability, expense and procedure duration have limited barostat use in clinical practice. To address these issues, recent efforts have been made to validate short barostat protocols^{234,235} and to develop simple bedside tests, such as the use of a portable device (Rapid Barostat Bag Pump, Mui Scientific, Canada).²³⁵

Areas for future research

1. Prospective, controlled studies are still required to establish the role of routine diagnostic investigations (e.g. transit study, tests of evacuation, and rectal sensitivity testing) and other measurement tools in stratifying treatment.

2. To further develop comprehensive testing to assess the relative importance of colonic motility, rectal motor-sensory function and patient behaviour at the level of the individual patient.
3. Large, preferably multicentre studies in healthy adults are needed to establish normal ranges of colonic motility patterns in response to standardised stimuli (meals, sleep, chemical stimulation).
4. MRI 'motility' techniques need to be further developed to cover all segments of the colon, thus avoiding the need for more invasive tests.
5. Given the acknowledged major overlap between health and CC,²²³ and poor agreement between results of different tests,^{144,224} the optimum method(s) for the diagnosis of dyssynergic defaecation requires re-evaluation.
6. Assessment of the impact of the London Classification for disorders of anorectal function; it is hoped that the use of a common language to describe results of diagnostic tests, standard operating procedures, and a consensus classification system will bring much-needed standardisation. This is projected to facilitate co-operation between centres and the performance of multi-centre studies, a key requirement if progress is to be made towards improved diagnosis and individually tailored therapy of patients with these conditions.

SUMMARY & CONCLUSIONS

Chronic constipation is common, problematic for the sufferer and complex for the physician. This review has sought to coalesce up-to-date information on several key aspects of CC. The content should provide an educational resource for the reader with a clinical or research interest in this disease area. It also frames the background for the sister review addressing therapy. It is hoped that some of the many areas of future research outlined will be addressed by a future generation of readers.

REFERENCES

1. Cook IJ, Talley NJ, Benninga MA, Rao SS, Scott SM. Chronic constipation: overview and challenges. *Neurogastroenterol Motil* 2009;21(Suppl 2):1-8.
2. Brookes SJ, Dinning PG, Gladman MA. Neuroanatomy and physiology of colorectal function and defaecation: from basic science to human clinical studies. *Neurogastroenterol Motil* 2009;21(Suppl 2):9-19.
3. Dinning PG, Smith TK, Scott SM. Pathophysiology of colonic causes of chronic constipation. *Neurogastroenterol Motil* 2009;21(Suppl 2):20-30.

4. Lunniss PJ, Gladman MA, Benninga MA, Rao SS. Pathophysiology of evacuation disorders. *Neurogastroenterol Motil* 2009;21(Suppl 2):31-40.
5. Emmanuel AV, Tack J, Quigley EM, Talley NJ. Pharmacological management of constipation. *Neurogastroenterol Motil* 2009;21(Suppl 2):41-54.
6. Whitehead WE, Di Lorenzo C, Leroi AM, Porrett T, Rao SS. Conservative and behavioural management of constipation. *Neurogastroenterol Motil* 2009;21(Suppl 2):55-61.
7. Knowles CH, Dinning PG, Pescatori M, Rintala R, Rosen H. Surgical management of constipation. *Neurogastroenterol Motil* 2009;21(Suppl 2):62-71.
8. Brandt LJ, Prather CM, Quigley EM, Schiller LR, Schoenfeld P, Talley NJ. Systematic review on the management of chronic constipation in North America. *Am J Gastroenterol* 2005;100(Suppl 1):S5-S21
9. Camilleri M, Ford AC, Mawe GM, et al. Chronic constipation. *Nat Rev Dis Primers* 2017;3:17095.
10. Soares NC, Ford AC. Prevalence of, and risk factors for, chronic idiopathic constipation in the community: Systematic review and meta-analysis. *Am J Gastroenterol* 2011;106:1582-1591.
11. Enck P, Aziz Q, Barbara G, et al. Irritable bowel syndrome. *Nat Rev Dis Primers* 2016;2:16014.
12. Gladman MA , Lunniss PJ, Scott SM, Swash M. Rectal hyposensitivity. *Am J Gastroenterol* 2006;101(5):1140-51.
13. Talley NJ, Fleming KC, Evans JM, et al. Constipation in an elderly community: A study of prevalence and potential risk factors. *Am J Gastroenterol* 1996;91:19-25.
14. Talley NJ, Weaver AL, Zinsmeister AR, Melton LJ, III. Functional constipation and outlet delay: A population-based study. *Gastroenterology* 1993;105:781-790.
15. Johanson JF, Sonnenberg A. The prevalence of hemorrhoids and chronic constipation. An epidemiologic study. *Gastroenterology* 1990;98:380-386.
16. Bytzer P, Howell S, Leemon M, Young LJ, Jones MP, Talley NJ. Low socioeconomic class is a risk factor for upper and lower gastrointestinal symptoms: A population based study in 15 000 Australian adults. *Gut* 2001;49:66-72.
17. Wald A, Scarpignato C, Kamm MA, et al. The burden of chronic constipation on quality of life: Results of a multinational survey. *Aliment Pharmacol Ther* 2007;26:227-236.
18. Drossman DA, Li Z, Andruzzi E, et al. U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. *Dig Dis Sci* 1993;38:1569-1580.
19. Bowel Interest Group. Cost of constipation report. <https://bowelinterestgroup.co.uk/cost-of-constipation-report-2019-hcps/>.
20. Lacy BE, Mearin F, Chang L, et al. Bowel disorders. *Gastroenterology* 2016;150:1393-1407.

21. Aziz I, Whitehead WE, Palsson OS, Tornblom H, Simren M. An approach to the diagnosis and management of Rome IV functional disorders of chronic constipation. *Expert Rev Gastroenterol Hepatol* 2020;14(1):39-46.
22. Rao SS, Rattanakovit K, Patcharatrakul T. Diagnosis and management of chronic constipation in adults. *Nat Rev Gastroenterol Hepatol* 2016;13:295-305.
23. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol* 1997;32:920-924.
24. Saad RJ, Rao SS, Koch KL, et al. Do stool form and frequency correlate with whole-gut and colonic transit? Results from a multicenter study in constipated individuals and healthy controls. *Am J Gastroenterol* 2010;105:403-411.
25. Khanna P, Agarwal N, Khanna D, et al. Development of an online library of patient-reported outcome measures in gastroenterology: the GI-PRO database. *Am J Gastroenterol* 2014;109:234-248.
26. Spiegel BM, Hays RD, Bolus R, et al. Development of the NIH Patient-Reported Outcomes Measurement Information System (PROMIS) gastrointestinal symptom scales. *Am J Gastroenterol* 2014;109:1804-14.
27. Nelson LM, Williams VS, Fehnel SE, et al. Psychometric validation of patient-reported outcome measures assessing chronic constipation. *Clin Exp Gastroenterol* 2014 Sep 26;7:385-94.
28. Ersoy O, Temel YE, Alptekin HK. Validity and reliability of the measure yourself medical outcome profile 2 (MYMOP2) questionnaire among Turkish patients having anorectal disorders. *Turk J Gastroenterol* 2019;30:28-32.
29. Frank L, Kleinman L, Farup C, Taylor L, Miner P, Jr. Psychometric validation of a constipation symptom assessment questionnaire. *Scand J Gastroenterol* 1999;34:870-877.
30. Agachan F, Chen T, Pfeifer J, Reissman P, Wexner SD. A constipation scoring system to simplify evaluation and management of constipated patients. *Dis Colon Rectum* 1996;39:681-685.
31. Knowles CH, Eccersley AJ, Scott SM, Walker SM, Reeves B, Lunniss PJ. Linear discriminant analysis of symptoms in patients with chronic constipation: validation of a new scoring system (KESS). *Dis Colon Rectum* 2000;43:1419-1426.
32. Rao SS, Bharucha AE, Chiarioni G, et al. Functional anorectal disorders. *Gastroenterology* 2016;150:1430-1442. e4.
33. Mihaylov S, Stark C, McColl E, et al. Stepped treatment of older adults on laxatives. The STOOL trial. *Health Technol Assess* 2008;12:iii-iv, ix-139.

34. Dimidi E, Cox C, Grant R, Scott SM, Whelan K. Perceptions of constipation among the general public and people with constipation differ strikingly from those of general and specialist doctors and the Rome IV criteria. *Am J Gastroenterol* 2019;114:1116-1129.
35. Moore-Gillon V. Constipation: what does the patient mean? *J R Soc Med* 1984;77:108-110.
36. Walter S, Hallbook O, Gotthard R, Bergmark M, Sjodahl R. A population-based study on bowel habits in a Swedish community: prevalence of faecal incontinence and constipation. *Scand J Gastroenterol* 2002;37:911-916.
37. Rey E, Balboa A, Mearin F. Chronic constipation, irritable bowel syndrome with constipation and constipation with pain/discomfort: similarities and differences. *Am J Gastroenterol* 2014;109:876-884.
38. Bharucha AE, Locke GR, Zinsmeister AR, et al. Differences between painless and painful constipation among community women. *Am J Gastroenterol* 2006;101:604-612.
39. Ford AC, Bercik P, Morgan DG, Bolino C, Pintos-Sanchez MI, Moayyedi P. Characteristics of functional bowel disorder patients: a cross-sectional survey using the Rome III criteria. *Aliment Pharmacol Ther* 2014;39:312-321.
40. Shekhar C, Monaghan PJ, Morris J, et al. Rome III functional constipation and irritable bowel syndrome with constipation are similar disorders within a spectrum of sensitization, regulated by serotonin. *Gastroenterology* 2013;145:749-757.
41. Wong RK, Palsson OS, Turner MJ, et al. Inability of the Rome III criteria to distinguish functional constipation from constipation-subtype irritable bowel syndrome. *Am J Gastroenterol* 2010;105:2228-2234.
42. Palsson OS, Baggish JS, Turner MJ, Whitehead WE. IBS patients show frequent fluctuations between loose/watery and hard/lumpy stools: implications for treatment. *Am J Gastroenterol* 2012;107:286-295.
43. Whitehead WE, Palsson OS, Simren M. Biomarkers to distinguish functional constipation from irritable bowel syndrome with constipation. *Neurogastroenterol Motil* 2016;28:783-792.
44. Vriesman MH, Koppen IJN, Camilleri M, Di Lorenzo C, Benninga MA. Management of functional constipation in children and adults. *Nat Rev Gastroenterol Hepatol* 2020;17:21-39.
45. Bongers MEJ, van Wijk MP, Reitsma JB, Benninga MA. Long- term prognosis for childhood constipation: clinical outcomes in adulthood. *Pediatrics* 2010;126:156-162.
46. Brooks AJ, Smith PJ, Cohen R, et al. UK guideline on transition of adolescent and young persons with chronic digestive diseases from paediatric to adult care. *Gut* 2017;66:988-1000.

47. Sattoe JNT, Peeters MAC, Haitisma J, van Staa A, Wolters VM, Escher JC. Value of an outpatient transition clinic for young people with inflammatory bowel disease: a mixed-methods evaluation. *BMJ Open* 2020;10:e033535.
48. Whitehead WE, Borrud L, Goode PS, et al. Fecal incontinence in US adults: epidemiology and risk factors. *Gastroenterology* 2009;137:512-517.
49. Ditah I, Devaki P, Luma HN, et al. Prevalence, trends, and risk factors for fecal incontinence in United States adults, 2005-2010. *Clin Gastroenterol Hepatol* 2014;12:636-643.e1-2
50. Sharma A, Yuan L, Marshall RJ, Merrie AE, Bissett IP. Systematic review of the prevalence of faecal incontinence. *Br J Surg* 2016;103:1589-1597.
51. Pares D, Vial M, Bohle B, et al. Prevalence of faecal incontinence and analysis of its impact on quality of life and mental health. *Colorectal Dis* 2011;13:899-905.
52. Rao SS. Pathophysiology of adult fecal incontinence. *Gastroenterology* 2004;126 (Suppl 1):S14-22.
53. Lunniss PJ, Gladman MA, Hetzer FH, Williams NS, Scott SM. Risk factors in acquired faecal incontinence. *J R Soc Med* 2004;97:111-116.
54. Bharucha AE, Zinsmeister AR, Locke GR, et al. Risk factors for fecal incontinence: a population-based study in women. *Am J Gastroenterol* 2006;101:1305-1312.
55. Bharucha AE, Zinsmeister AR, Schleck CD, Melton LJ 3rd. Bowel disturbances are the most important risk factors for late onset fecal incontinence: a population-based case-control study in women. *Gastroenterology* 2010;139:1559-1566.
56. Loening-Baucke V. Prevalence rates for constipation and faecal and urinary incontinence. *Arch Dis Child* 2007;92:486-489.
57. Rajindrajith S, Devanarayana NM, Benninga MA. Review article: faecal incontinence in children: epidemiology, pathophysiology, clinical evaluation and management. *Aliment Pharmacol Ther* 2013;37:37-48.
58. Madoff RD, Williams JG, Caushaj PF. Fecal incontinence. *N Engl J Med* 1992;326: 1002-1007.
59. Romero Y, Evans JM, Fleming KC, Phillips SF. Constipation and fecal incontinence in the elderly population. *Mayo Clin Proc* 1996;71:81-92.
60. Nurko S, Scott SM. Coexistence of constipation and incontinence in children and adults. *Best Pract Res Clin Gastroenterol* 2011;25:29-41.
61. Damon H, Guye O, Seigneurin A, et al. Prevalence of anal incontinence in adults and impact on quality-of-life. *Gastroenterol Clin Biol* 2006;30:37-43.

62. Mohammed SD, Lunniss PJ, Zarate N, et al. Joint hypermobility and rectal evacuatory dysfunction: an etiological link in abnormal connective tissue? *Neurogastroenterol Motil* 2010;22:1085-e283.
63. Brochard C, Chambaz M, Ropert A, et al. Quality of life in 1870 patients with constipation and/or fecal incontinence: Constipation should not be underestimated. *Clin Res Hepatol Gastroenterol* 2019;43:682-687.
64. Cauley CE, Savitt LR, Weinstein M, et al. A quality-of-life comparison of two fecal incontinence phenotypes: isolated fecal incontinence versus concurrent fecal incontinence with constipation. *Dis Colon Rectum* 2019;62:63-70.
65. Vollebregt PF, Wiklendt L, Dinning PG, Knowles CH, Scott SM. Coexistent faecal incontinence and constipation: a cross-sectional study of 4,027 adults undergoing specialist assessment. *EClinicalMedicine* 2020: in press
66. Clayden G, Wright A. Constipation and incontinence in childhood: two sides of the same coin? *Arch Dis Child* 2007;92:472-474.
67. Swash M, Snooks SJ, Henry MM. Unifying concept of pelvic floor disorders and incontinence. *J R Soc Med* 1985;78:906-11.
68. Petros P, Swash M. The musculo-elastic theory of anorectal function and dysfunction. *Pelviperrineology* 2008;27:89-93.
69. Verduron A, Devroede G, Bouchoucha M, et al. Megarectum. *Dig Dis Sci* 1988;33:1164-1174.
70. Gladman MA, Scott SM, Chan CL, Williams NS, Lunniss PJ. Rectal hyposensitivity: prevalence and clinical impact in patients with intractable constipation and fecal incontinence. *Dis Colon Rectum* 2003;46:238–246.
71. Rex DK, Lappas JC. Combined anorectal manometry and defecography in 50 consecutive adults with fecal incontinence. *Dis Colon Rectum* 1992;35:1040–1045.
72. Hawkins AT, Olariu AG, Savitt LR, et al. Impact of rising grades of internal rectal intussusception on fecal continence and symptoms of constipation. *Dis Colon Rectum* 2016;59:54-61.
73. Rao SS, Ozturk R, Stessman M. Investigation of the pathophysiology of fecal seepage. *Am J Gastroenterol* 2004;99:2204-2209.
74. Slawik S, Soulsby R, Carter H, Payne H, Dixon AR. Laparoscopic ventral rectopexy, posterior colporrhaphy and vaginal sacrocolpopexy for the treatment of recto-genital prolapse and mechanical outlet obstruction. *Colorectal Dis* 2008;10:138-143.
75. Sung VW, Rardin CR, Raker CA, LaSala CA, Myers DL. Changes in bowel symptoms 1 year after rectocele repair. *Am J Obstet Gynecol* 2012;207:423.e1-5

76. Formijne Jonkers HA, Poierrié N, Draaisma WA, Broeders IA, Consten EC. Laparoscopic ventral rectopexy for rectal prolapse and symptomatic rectocele: an analysis of 245 consecutive patients. *Colorectal Dis* 2013;15:695-699.
77. Koch SM, Melenhorst J, van Gemert WG, Baeten CG. Prospective study of colonic irrigation for the treatment of defaecation disorders. *Br J Surg* 2008;95:1273-1279.
78. Sallam H, McNearney TA, Chen JD. Systematic review: pathophysiology and management of gastrointestinal dysmotility in systemic sclerosis (scleroderma). *Aliment Pharmacol Ther* 2006;23:691-712.
79. Beckers AB, Keszthelyi D, Fikree A, et al. Gastrointestinal disorders in joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type: a review for the gastroenterologist. *Neurogastroenterol Motil* 2017;29:e13013.
80. De Wandele I, Rombaut L, Malfait F, De Backer T, De Paepe A, Calders P. Clinical heterogeneity in patients with the hypermobility type of Ehlers-Danlos syndrome. *Res Dev Disabil* 2013;34:873-881.
81. Wang SJ, Lan JL, Chen DY, Chen YH, Hsieh TY, Lin WY. Colonic transit disorders in systemic sclerosis. *Clin Rheumatol* 2001;20:251-254.
82. Basilisco G, Barbera R, Vanoli M, Bianchi P. Anorectal dysfunction and delayed colonic transit in patients with progressive systemic sclerosis. *Dig Dis Sci* 1993;38:1525-1529.
83. Vigone B, Caronni M, Severino A, et al. Preliminary safety and efficacy profile of prucalopride in the treatment of systemic sclerosis (SSc)-related intestinal involvement: results from the open label cross-over PROGASS study. *Arthritis Res Ther* 2017;19:145.
84. Madsen JL, Hendel L. Gastrointestinal transit times of radiolabeled meal in progressive systemic sclerosis. *Dig Dis Sci* 1992;37:1404-1408.
85. Heyt GJ, Oh MK, Alemzadeh N, et al. Impaired rectoanal inhibitory response in scleroderma (systemic sclerosis): an association with fecal incontinence. *Dig Dis Sci* 2004;49:1040-1045.
86. Kim KC, Park HJ, Lee SK, et al. Anorectal dysfunction in systemic sclerosis. *J Korean Med Sci* 1996;11:244-249.
87. Thoua NM, Abdel-Halim M, Forbes A, Denton CP, Emmanuel AV. Fecal incontinence in systemic sclerosis is secondary to neuropathy. *Am J Gastroenterol* 2012;107:597-603.
88. Nelson AD, Mouchli MA, Valentin N, et al. Ehlers Danlos syndrome and gastrointestinal manifestations: a 20-year experience at Mayo Clinic. *Neurogastroenterol Motil* 2015;27:1657-1666.

89. Fikree A, Aziz Q, Ahmed M, Mohammed S, Knowles CH, Scott M. Joint hypermobility syndrome, rectal hyposensitivity and severe constipation in young nulliparous females. *Gut* 2013;62(Suppl 1):A98. (Abstract)
90. Fikree A, Grahame R, Aktar R, et al. A prospective evaluation of undiagnosed joint hypermobility syndrome in patients with gastrointestinal symptoms. *Clin Gastroenterol Hepatol* 2014;12:1680-1687.
91. Zeitoun JD, Lefevre JH, de Parades V, et al. Functional digestive symptoms and quality of life in patients with Ehlers-Danlos syndromes: results of a national cohort study on 134 patients. *PLoS One* 2013;8:e80321.
92. McFarlane IM, Bhamra MS, Kreps A, et al. Gastrointestinal manifestations of systemic sclerosis. *Rheumatology (Sunnyvale)* 2018;8:235.
93. Burcharth J, Rosenberg J. Gastrointestinal surgery and related complications in patients with Ehlers-Danlos syndrome: a systematic review. *Dig Surg* 2012;29:349-357.
94. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68(6):394–424
95. Emmertsen KJ, Laurberg S. Low anterior resection syndrome score: development and validation of a symptom-based scoring system for bowel dysfunction after low anterior resection for rectal cancer. *Ann Surg* 2012;255:922-928.
96. Bryant CLC, Lunniss PJ, Knowles CH, Thaha MA, Chan CLH. Anterior resection syndrome. *Lancet Oncol* 2012;13:e403–408.
97. Emmertsen KJ, Laurberg S. Impact of bowel dysfunction on quality of life after sphincter-preserving resection for rectal cancer. *Br J Surg* 2013;100:1377–1387.
98. Pieniowski E, Palmer G, Juul T, Lagergren P, Johar A. Low anterior resection syndrome and quality of life after sphincter-sparing rectal cancer surgery: a long-term longitudinal follow up. *Dis Colon Rectum* 2019;62:14–20.
99. van Heinsbergen M, den Haan N, Maaskant-Braat AJ, et al. Functional bowel complaints and quality of life after surgery for colon cancer: prevalence and predictive factors. *Colorectal Dis* 2020;22:136-145.
100. Levack MM, Savitt LR, Berger DL, et al. Sigmoidectomy syndrome? Patients' perspectives on the functional outcomes following surgery for diverticulitis. *Dis Colon Rectum* 2012;55:10-17.
101. Bregendahl S, Emmertsen KJ, Fassov J, et al. Neorectal hyposensitivity after neoadjuvant therapy for rectal cancer. *Radiother Oncol* 2013;108:331–336.

102. Horgan PG, O'Connell PR, Shinkwin CA, Kirwan WO. Effect of anterior resection on anal sphincter function. *Br J Surg* 1989;76:783–786.
103. Lorenzi B, Brading AF, Martellucci J, Cetta F, Mortensen NJ. Short-term effects of neoadjuvant chemoradiotherapy on internal anal sphincter function: a human in vitro study. *Dis Colon Rectum* 2012;55:465–472.
104. Iizuka I, Koda K, Seike K, et al. Defecatory malfunction caused by motility disorder of the neorectum after anterior resection for rectal cancer. *Am J Surg* 2004;188:176–180.
105. Lee WY, Takahashi T, Pappas T, Mantyh CR, Ludwig KA. Surgical autonomic denervation results in altered colonic motility: an explanation for low anterior resection syndrome? *Surgery* 2008;143:778–83.
106. Glare P, Walsh D, Sheehan D. The adverse effects of morphine: a prospective survey of common symptoms during repeated dosing for chronic cancer pain. *Am J Hosp Palliat Care* 2006;23:229-235.
107. Tuteja AK, Biskupiak J, Stoddard GJ, Lipman AG. Opioid-induced bowel disorders and narcotic bowel syndrome in patients with chronic non-cancer pain. *Neurogastroenterol Motil* 2010;22:424-430, e496.
108. Drewes AM, Munkholm P, Simren M, et al. Definition, diagnosis and treatment strategies for opioid-induced bowel dysfunction-Recommendations of the Nordic Working Group. *Scand J Pain* 2016;11:111-122.
109. Bell T, Annunziata K, Leslie JB. Opioid-induced constipation negatively impacts pain management, productivity, and health-related quality of life: findings from the National Health and Wellness Survey. *J Opioid Manag* 2009;5:137-144.
110. Ducrotte P, Milce J, Soufflet C, Fabry C. Prevalence and clinical features of opioid-induced constipation in the general population: A French study of 15,000 individuals. *United European Gastroenterol J* 2017;5:588-600.
111. Gupta A, Coyne KS, Datto C, Venuti C. The burden of opioid-induced constipation in younger patients with chronic noncancer pain. *Pain Med* 2018;19:2459-2468.
112. Nojkov B, Baker J, Menees S, et al. Is dyssynergic defecation an unrecognized cause of chronic constipation in patients using opioids? *Am J Gastroenterol* 2019;114:1772-1777.
113. Vollebregt PF, Hooper RL, Farmer AD, Miller J, Knowles CH, Scott SM. Association between opioid usage and rectal dysfunction in constipation: A cross-sectional study of 2754 patients. *Neurogastroenterol Motil* 2020:e13839 (Online ahead of print)
114. Drossman DA, Leserman J, Nachman G, et al. Sexual and physical abuse in women with functional or organic gastrointestinal disorders. *Ann Intern Med* 1990;113:828-833.

115. Farnam A, Somi MH, Sarami F, Farhang S, Yasrebinia S. Personality factors and profiles in variants of irritable bowel syndrome. *World J Gastroenterol* 2007;13:6414-6418.
116. Koloski NA, Jones M, Kalantar J, Weltman M, Zaguirre J, Talley NJ. The brain-gut pathway in functional gastrointestinal disorders is bidirectional: a 12-year prospective population-based study. *Gut* 2012;61:1284-1290.
117. Jones MP, Tack J, Van Oudenhove L, et al. Mood and anxiety disorders precede development of functional gastrointestinal disorders in patients but not in the population. *Clin Gastroenterol Hepatol* 2017;15:1014-1020 e1014.
118. Zarate N, Knowles CH, Newell M, et al. In patients with slow transit constipation, the pattern of colonic transit delay does not differentiate between those with and without impaired rectal evacuation. *Am J Gastroenterol* 2008;103:427-434.
119. Bassotti G, Gaburri M, Imbimbo BP, et al. Colonic mass movements in idiopathic chronic constipation. *Gut* 1988;29:1173-1179.
120. Rao SS, Sadeghi P, Beaty J, Kavlock R. Ambulatory 24-hour colonic manometry in slow-transit constipation. *Am J Gastroenterol* 2004;99:2405-2416.
121. Dinning PG, Zarate N, Hunt LM, et al. Pancolonic spatiotemporal mapping reveals regional deficiencies in, and disorganization of colonic propagating pressure waves in severe constipation. *Neurogastroenterol Motil* 2010;22:e340-349.
122. Corsetti M, Pagliaro G, Demedts I, et al. Pan-colonic pressurizations associated with relaxation of the anal sphincter in health and disease: a new colonic motor pattern identified using high-resolution manometry. *Am J Gastroenterol* 2017;112:479-489.
123. Dinning PG, Wiklendt L, Maslen L, et al. Colonic motor abnormalities in slow transit constipation defined by high resolution, fibre-optic manometry. *Neurogastroenterol Motil* 2015;27:379-388.
124. Zikos TA, Kamal AN, Neshatian L, et al. High prevalence of slow transit constipation in patients with gastroparesis. *J Neurogastroenterol Motil* 2019;25:267-275.
125. Shahid S, Ramzan Z, Maurer AH, Parkman HP, Fisher RS. Chronic idiopathic constipation: more than a simple colonic transit disorder. *J Clin Gastroenterol* 2012;46:150-154.
126. Scott SM, Picon L, Knowles CH, et al. Automated quantitative analysis of nocturnal jejunal motor activity identifies abnormalities in individuals and subgroups of patients with slow transit constipation. *Am J Gastroenterol* 2003;98:1123-1134.
127. Seidl H, Gundling F, Pehl C, Pfeiffer A, Schepp W, Schmidt T. Small bowel motility in functional chronic constipation. *Neurogastroenterol Motil* 2009;21:1278-e1122.
128. Zarate N, Knowles CH, Yazaki E, Lunnis PJ, Scott SM. Clinical presentation and patterns of slow transit constipation do not predict coexistent upper gut dysmotility. *Dig Dis Sci* 2009;54:122-31.

129. Carrington EV, Scott SM, Bharucha A, et al. Expert consensus document: Advances in the evaluation of anorectal function. *Nat Rev Gastroenterol Hepatol* 2018;15:309-323.
130. Johanson JF, Kralstein J. Chronic constipation: a survey of the patient perspective. *Aliment Pharmacol Ther* 2007;25:599-608.
131. Grossi U, Di Tanna GL, Heinrich H, Taylor SA, Knowles CH, Scott SM. Systematic review with meta-analysis: defecography should be a first-line diagnostic modality in patients with refractory constipation. *Aliment Pharmacol Ther* 2018;48:1186-1201.
132. D'Hoore A, Penninckx F. Obstructed defecation. *Colorect Dis* 2003;5:280-287.
133. Mellgren A, Bremmer S, Johansson C, et al. Defecography. Results of investigations in 2,816 patients. *Dis Colon Rectum* 1994;37:1133-1141.
134. Agachan F, Pfeifer J, Wexner SD. Defecography and proctography. Results of 744 patients. *Dis Colon Rectum* 1996;39:899-905.
135. Preston DM, Lennard-Jones JE. Anismus in chronic constipation. *Dig Dis Sci* 1985;30:413-418.
136. Shouler P, Keighley MRB. Changes in colorectal function in severe idiopathic chronic constipation. *Gastroenterology* 1986;90:414-420.
137. Turnbull GK, Lennard-Jones JE, Bartram CI. Failure of rectal expulsion as a cause of constipation: why fibre and laxatives sometimes fail. *Lancet* 1986;1:767-769.
138. Yu T, Qian D, Zheng Y, Jiang Y, Wu P, Lin L. Rectal hyposensitivity is associated with a defecatory disorder but not delayed colon transit time in a functional constipation population. *Medicine (Baltimore)* 2016;95:e3667.
139. Bharucha AE, Fletcher JG, Seide B, Riederer SJ, Zinsmeister AR. Phenotypic variation in functional disorders of defecation. *Gastroenterology* 2005;128:1199-1210.
140. Staller K, Barshop K, Kuo B, Ananthakrishnan AN. Resting anal pressure, not outlet obstruction or transit, predicts healthcare utilization in chronic constipation: a retrospective cohort analysis. *Neurogastroenterol Motil* 2015;27:1378-1388.
141. Ragg J, McDonald R, Hompes R, Jones OM, Cunningham C, Lindsey I. Isolated colonic inertia is not usually the cause of chronic constipation. *Colorectal Dis* 2011;13:1299-1302.
142. Rao SS, Ozturk R, Laine L. Clinical utility of diagnostic tests for constipation in adults: a systematic review. *Am J Gastroenterol* 2005;100:1605-1615.
143. Videlock EJ, Lembo A, Cremonini F. Diagnostic testing for dyssynergic defecation in chronic constipation: meta-analysis. *Neurogastroenterol Motil* 2013;25:509-520.
144. Palit S, Thin N, Knowles CH, Lunniss PJ, Bharucha AE, Scott SM. Diagnostic disagreement between tests of evacuatory function: a prospective study of 100 constipated patients. *Neurogastroenterol Motil* 2016;28:1589-1598.

145. Goyal O, Bansal M, Sood A. Clinical and anorectal manometry profile of patients with functional constipation and constipation-predominant irritable bowel syndrome. *Indian J Gastroenterol* 2019;38:211-219.
146. Vollebregt PF, Burgell RE, Hooper RL, Knowles CH, Scott SM. Clinical impact of rectal hyposensitivity: a cross-sectional study of 2,876 patients with refractory functional constipation. *Am J Gastroenterol* 2020: in press.
147. Gunterberg B, Kewenter J, Petersen I, et al. Anorectal function after major resections of the sacrum with bilateral or unilateral sacrifice of sacral nerves. *Br J Surg* 1976;63:546-554.
148. Sun WM, MacDonagh R, Forster D, et al. Anorectal function in patients with complete spinal transection before and after sacral posterior rhizotomy. *Gastroenterology* 1995;108:990-8.
149. Lynch AC, Anthony A, Dobbs BR, Frizelle FA. Anorectal physiology following spinal cord injury. *Spinal Cord* 2000;38:573-580.
150. Pannek J, Greving I, Tegenthoff M, et al. Urodynamic and rectomanometric findings in patients with spinal cord injury. *Neurourol Urodyn* 2001;20:95-103.
151. Cheng J, Li L, Xu F, Xu Y, Lin L, Chen JDZ. Poststroke constipation is associated with impaired rectal sensation. *Am J Gastroenterol* 2020;115:105-114.
152. Nordenbo AM, Andersen JR, Andersen JT. Disturbances of ano-rectal function in multiple sclerosis. *J Neurol* 1996;243:445-451.
153. Scott SM, van den Berg MM, Benninga MA. Rectal sensorimotor dysfunction in constipation. *Best Pract Res Clin Gastroenterol* 2011;25:103-118.
154. Scott SM, Lunniss PJ. Rectal hyposensitivity and functional hindgut disorders: cause and effect or an epiphenomenon? *J Pediatr Gastroenterol Nutr* 2011;53(Suppl 2):S47-9.
155. Gladman MA, Aziz Q, Scott SM, Williams NS, Lunniss PJ. Rectal hyposensitivity: pathophysiological mechanisms. *Neurogastroenterol Motil* 2009;21:508-516, e504-505.
156. Harraf F, Schmulson M, Saba L, et al. Subtypes of constipation predominant irritable bowel syndrome based on rectal perception. *Gut* 1998;43:388-394.
157. Agrawal A, Houghton LA, Lea R, Morris J, Reilly B, Whorwell PJ. Bloating and distention in irritable bowel syndrome: the role of visceral sensation. *Gastroenterology* 2008;134:1882-1889.
158. Wijffels NA, Angelucci G, Ashrafi A, Jones OM, Cunningham C, Lindsey I. Rectal hyposensitivity is uncommon and unlikely to be the central cause of obstructed defecation in patients with high-grade internal rectal prolapse. *Neurogastroenterol Motil* 2011;23:151-154, e130.
159. Schouten WR, Gosselink MJ, Boerma MO, Ginai AZ. Rectal wall contractility in response to an evoked urge to defecate in patients with obstructed defecation. *Dis Colon Rectum* 1998;41:473-479.

160. Kellow JE, Gill RC, Wingate DL. Modulation of human upper gastrointestinal motility by rectal distension. *Gut* 1987;28:864-868.
161. Mollen RM, Salvioli B, Camilleri M, et al. The effects of biofeedback on rectal sensation and distal colonic motility in patients with disorders of rectal evacuation: evidence of an inhibitory rectocolonic reflex in humans? *Am J Gastroenterol* 1999;94:751-756.
162. Preston DM, Lennard-Jones JE. Severe chronic constipation of young women: 'idiopathic slow transit constipation'. *Gut* 1986;27:41-48.
163. Chaussade S, Khyari A, Roche H, et al. Determination of total and segmental colonic transit time in constipated patients - results in 91 patients with a new simplified method. *Dig Dis Sci* 1989;34:1168-1172.
164. Knowles CH, Scott SM, Wellmer A, et al. Sensory and autonomic neuropathy in patients with idiopathic slow-transit constipation. *Br J Surg* 1999;86:54-60.
165. Salomon R, Attie T, Pelet A, et al. Germline mutations of the RET ligand GDNF are not sufficient to cause Hirschsprung disease. *Nat Genet* 1996;14:345-347.
166. Knowles CH, Gayther SA, Scott M, et al. Idiopathic slow-transit constipation is not associated with mutations of the RET proto-oncogene or GDNF. *Dis Colon Rectum* 2000;43:851-857.
167. Wouters MM, Lambrechts D, Knapp M, et al. Genetic variants in CDC42 and NXP1 as susceptibility factors for constipation and diarrhoea predominant irritable bowel syndrome. *Gut* 2014;63:1103-1111.
168. Knowles CH, Veress B, Kapur RP, et al. Quantitation of cellular components of the enteric nervous system in the normal human gastrointestinal tract--report on behalf of the Gastro 2009 International Working Group. *Neurogastroenterol Motil* 2011;23:115-124.
169. Smith B, Grace RH, Todd IP. Organic constipation in adults. *Br J Surg* 1977;64:313-314.
170. Krishnamurthy S, Schuffler MD, Rohrmann CA, Pope CE. Severe idiopathic constipation is associated with a distinctive abnormality of the colonic myenteric plexus. *Gastroenterology* 1985;88:26-34.
171. Knowles CH, Farrugia G. Gastrointestinal neuromuscular pathology in chronic constipation. *Best Pract Res Clin Gastroenterol* 2011;25:43-57.
172. Wedel T, Roblick UJ, Ott V, et al. Oligoneuronal hypoganglionosis in patients with idiopathic slow-transit constipation. *Dis Colon Rectum* 2002;45:54-62.
173. Dimidi E, Christodoulides S, Scott SM, Whelan K. Mechanisms of action of probiotics and the gastrointestinal microbiota on gut motility and constipation. *Adv Nutr* 2017;8:484-494.

174. Parthasarathy G, Chen J, Chen X, et al. Relationship between microbiota of the colonic mucosa vs feces and symptoms, colonic transit, and methane production in female patients with chronic constipation. *Gastroenterology* 2016;150:367-379 e361.
175. Lewis SJ, Heaton KW. Increasing butyrate concentration in the distal colon by accelerating intestinal transit. *Gut* 1997;41:245-251.
176. Wolf PG, Parthasarathy G, Chen J, et al. Assessing the colonic microbiome, hydrogenogenic and hydrogenotrophic genes, transit and breath methane in constipation. *Neurogastroenterol Motil* 2017;29:1-9.
177. Lee KM, Paik CN, Chung WC, Yang JM, Choi MG. Breath methane positivity is more common and higher in patients with objectively proven delayed transit constipation. *Eur J Gastroenterol Hepatol* 2013;25:726-732.
178. Attaluri A, Jackson M, Paulson J, Rao SSC. Methanogenic flora is associated with altered colonic transit but not stool characteristics in constipation without IBS. *Am J Gastroenterol* 2010;105:1407-1411.
179. Shah A, Talley NJ, Jones M, et al. Small intestinal bacterial overgrowth in irritable bowel syndrome: a systematic review and meta-analysis of case-control studies. *Am J Gastroenterol* 2020;115:190-201.
180. Singh P, Duehren S, Katon J, et al. Breath methane does not correlate with constipation severity or bloating in patients with constipation. *J Clin Gastroenterol* 2020;54:365-369.
181. Kashyap PC, Marcobal A, Ursell LK, et al. Complex interactions among diet, gastrointestinal transit, and gut microbiota in humanized mice. *Gastroenterology* 2013;144:967-977.
182. Akervall S, Fasth S, Nordgren S, Oresland T, Hulten L. The functional results after colectomy and ileorectal anastomosis for severe constipation (Arbuthnot Lane's disease) as related to rectal sensory function. *Int J Colorectal Dis* 1988;3:96-101.
183. Narayanan SP, Bharucha AE. A practical guide to biofeedback therapy for pelvic floor disorders. *Curr Gastroenterol Rep* 2019;21:21.
184. Rao SS, Welcher KD, Pelsang RE. Effects of biofeedback therapy on anorectal function in obstructive defecation. *Dig Dis Sci* 1997;42:2197-2205.
185. Peticca L, Pescatori M. Outlet obstruction due to anismus and rectal hyposensation: effect of biofeedback training. *Colorectal Dis* 2002;4:67.
186. Bharucha AE, Dorn SD, Lembo A, Pressman A. American Gastroenterological Association medical position statement on constipation. *Gastroenterology* 2013;144:211-217.
187. Fox MR, Kahrilas PJ, Roman S, et al. Clinical measurement of gastrointestinal motility and function: who, when and which test? *Nat Rev Gastroenterol Hepatol* 2018;15:568-579.

188. Wang YT, Mohammed SD, Farmer AD, et al. Regional gastrointestinal transit and pH studied in 215 healthy volunteers using the wireless motility capsule: influence of age, gender, study country and testing protocol. *Aliment Pharmacol Ther* 2015;42:761-772.
189. Evans RC, Kamm MA, Hinton JM, Lennard-Jones JE. The normal range and a simple diagram for recording whole gut transit time. *Int J Colorectal Dis* 1992;7:15-17.
190. Cowlam S, Vinayagam R, Khan U, et al. Blinded comparison of faecal loading on plain radiography versus radio-opaque marker transit studies in the assessment of constipation. *Clin Radiol* 2008;63:1326-1331.
191. Metcalf AM, Phillips SF, Zinsmeister AR, MacCarty RL, Beart RW, Wolff BG. Simplified assessment of segmental colonic transit. *Gastroenterology* 1987;92:40-47.
192. Abrahamsson H, Antov S, Bosaeus I. Gastrointestinal and colonic segmental transit time evaluated by a single abdominal x-ray in healthy subjects and constipated patients. *Scand J Gastroenterol Suppl* 1988;152:72-80.
193. Nandhra GK, Mark EB, Di Tanna GL, et al. Normative values for region-specific colonic and gastrointestinal transit times in 111 healthy volunteers using the 3D-Transit electromagnet tracking system: Influence of age, gender, and body mass index. *Neurogastroenterol Motil* 2020;32:e13734.
194. Rao SS, Camilleri M, Hasler WL, et al. Evaluation of gastrointestinal transit in clinical practice: position paper of the American and European Neurogastroenterology and Motility Societies. *Neurogastroenterol Motil* 2011;23:8-23.
195. Krevsky B, Malmud LS, D'Ercole F, Maurer AH, Fisher RS. Colonic transit scintigraphy: a physiologic approach to the quantitative measurement of colonic transit in humans. *Gastroenterology* 1986;91:1102-1112.
196. Bonapace ES, Maurer AH, Davidoff S, Krevsky B, Fisher RS, Parkman HP. Whole gut transit scintigraphy in the clinical evaluation of patients with upper and lower gastrointestinal symptoms. *Am J Gastroenterol* 2000;95:2838-2847.
197. Camilleri M, Thorne NK, Ringel Y, et al. Wireless pH-motility capsule for colonic transit: prospective comparison with radiopaque markers in chronic constipation. *Neurogastroenterol Motil* 2010;22:874-e233.
198. Zarate N, Mohammed SD, O'Shaughnessy E, et al. Accurate localization of a fall in pH within the ileocecal region: validation using a dual-scintigraphic technique. *Am J Physiol Gastrointest Liver Physiol* 2010;299:G1276-G1286.
199. Mark EB, Poulsen JL, Haase AM, et al. Ambulatory assessment of colonic motility using the electromagnetic capsule tracking system. *Neurogastroenterol Motil* 2019;31:e13451.

200. Bampton PA, Dinning PG. High resolution colonic manometry—what have we learnt? A review of the literature 2012. *Curr Gastroenterol Rep* 2013;15:328.
201. Dinning PG, Carrington EV, Scott SM. The use of colonic and anorectal high-resolution manometry and its place in clinical work and in research. *Neurogastroenterol Motil* 2015;27:1693-1708.
202. Corsetti M, Costa M, Bassotti G, et al. First translational consensus on terminology and definitions of colonic motility in animals and humans studied by manometric and other techniques. *Nat Rev Gastroenterol Hepatol* 2019;16:559-579.
203. Dinning PG, Wiklendt L, Gibbins I, et al. Low-resolution colonic manometry leads to a gross misinterpretation of the frequency and polarity of propagating sequences: initial results from fiber-optic high-resolution manometry studies. *Neurogastroenterol Motil* 2013;25:e640-e649.
204. Kirchhoff S, Nicolaus M, Schirra J, Reiser MF, Göke B, Lienemann A. Assessment of colon motility using simultaneous manometric and functional cine-MRI analysis: preliminary results. *Abdom Imaging* 2011;36:24-30.
205. Pritchard SE, Paul J, Major G, et al. Assessment of motion of colonic contents in the human colon using MRI tagging. *Neurogastroenterol Motil* 2017;29:e13091.
206. Menys A, Hoad C, Spiller R, et al. Spatio-temporal motility MRI analysis of the stomach and colon. *Neurogastroenterol Motil* 2019;31:e13557.
207. Lam C, Chaddock G, Marciani L, et al. Colonic response to laxative ingestion as assessed by MRI differs in constipated irritable bowel syndrome compared to functional constipation. *Neurogastroenterol Motil* 2016;28:861-870.
208. Chaddock G, Lam C, Hoad C, et al. Novel MRI tests of orocecal transit time and whole gut transit time: studies in normal subjects. *Neurogastroenterol Motil* 2014;26:205-214.
209. Pritchard SE, Marciani L, Garsed K, et al. Fasting and postprandial volumes of the undisturbed colon: normal values and changes in diarrhea-predominant irritable bowel syndrome measured using serial MRI. *Neurogastroenterol Motil* 2014;26:124-130.
210. Chiarioni G, Kim SM, Vantini I, Whitehead WE. Validation of the balloon evacuation test: reproducibility and agreement with findings from anorectal manometry and electromyography. *Clin Gastroenterol Hepatol* 2014;12:2049-2054.
211. Minguez M, Herreros B, Sanchiz V, et al. Predictive value of the balloon expulsion test for excluding the diagnosis of pelvic floor dyssynergia in constipation. *Gastroenterology* 2004;126:57-62.

212. Chiarioni G, Salandini L, Whitehead WE. Biofeedback benefits only patients with outlet dysfunction, not patients with isolated slow transit constipation. *Gastroenterology* 2005;129:86-97.
213. Fletcher JG, Busse R, Riederer SJ, et al. Magnetic resonance imaging of anatomic and dynamic defects of the pelvic floor in defecatory disorders. *Am J Gastroenterol* 2003;98:399-411.
214. Mortelet KJ, Fairhurst J. Dynamic MR defecography of the posterior compartment: indications, techniques and MRI features. *Eur J Radiol* 2007;61:462-472.
215. Schawkat K, Heinrich H, Parker HL, et al. How to define pathologic pelvic floor descent in MR defecography during defecation? *Abdom Radiol (NY)* 2018;43:3233-3240.
216. Bertschinger KM, Hetzer FH, Roos JE, Treiber K, Marincek B, Hilfiker PR. Dynamic MR imaging of the pelvic floor performed with patient sitting in an open-magnet unit versus with patient supine in a closed-magnet unit. *Radiology* 2002;223:501-508.
217. Martellucci J, Naldini G. Clinical relevance of transperineal ultrasound compared with evacuation proctography for the evaluation of patients with obstructed defaecation. *Colorectal Dis* 2011;13:1167-1172.
218. Murad-Regadas SM, Regadas Filho FS, Regadas FS, et al. Use of dynamic 3-dimensional transvaginal and transrectal ultrasonography to assess posterior pelvic floor dysfunction related to obstructed defecation. *Dis Colon Rectum* 2014;57:228-236.
219. Carrington EV, Heinrich H, Knowles CH, et al. The international anorectal physiology working group (IAPWG) recommendations: standardized testing protocol and the London classification for disorders of anorectal function. *Neurogastroenterol Motil* 2020;32:e13679.
220. Rao SS, Kavlock R, Rao S. Influence of body position and stool characteristics on defecation in humans. *Am J Gastroenterol* 2006;101:2790-2796.
221. Wu GJ, Xu F, Lin L, Pasricha PJ, Chen JDZ. Anorectal manometry: should it be performed in a seated position? *Neurogastroenterol Motil* 2017;29:e12977.
222. Sharma M, Muthyala A, Feuerhak K, et al. Improving the utility of high-resolution manometry for the diagnosis of defecatory disorders in women with chronic constipation. *Neurogastroenterol Motil* 2020;32:e13910
223. Grossi U, Carrington EV, Bharucha AE, Horrocks EJ, Scott SM, Knowles CH. Diagnostic accuracy study of anorectal manometry for diagnosis of dyssynergic defecation. *Gut* 2016;65:447-455.
224. Heinrich H, Sauter M, Fox M, et al. Assessment of obstructive defecation by high-resolution anorectal manometry compared with magnetic resonance defecography. *Clin Gastroenterol Hepatol* 2015;13:1310-1317 e1.

225. Gregersen H, Chen SC, Leung WW, et al. Novel fecobionics defecatory function testing. *Clin Transl Gastroenterol* 2019;10:e00108.
226. Scott SM, Gladman MA. Manometric, sensorimotor, and neurophysiologic evaluation of anorectal function. *Gastroenterol Clin North Am* 2008;37:511-538.
227. Sun WM, Read NW, Prior A, Daly J-A, Cheah SK, Grundy D. Sensory and motor responses to rectal distention vary according to rate and pattern of balloon inflation. *Gastroenterology* 1990;99:1008-1015.
228. Gladman MA, Dvorkin LS, Lunniss PJ, Williams NS, Scott SM. Rectal hyposensitivity: a disorder of the rectal wall or the afferent pathway? An assessment using the barostat. *Am J Gastroenterol* 2005;100:106-114.
229. Whitehead WE, Delvaux M. Standardization of barostat procedures for testing smooth muscle tone and sensory thresholds in the gastrointestinal tract. *Dig Dis Sci* 1997;42:223-241.
230. Gregersen H. Standardization of barostat procedures. *Dig Dis Sci* 1998;43:1416-1420.
231. Fox M, Thumshirn M, Fried M, Schwizer W. Barostat measurement of rectal compliance and capacity. *Dis Colon Rectum* 2006;49:360-370.
232. Fox M, Thumshirn M, Fruhauf H, Fried M, Schwizer W. Determinants of fecal continence in healthy, continent subjects: a comprehensive analysis by anal manometry, rectal barostat and a stool substitute retention test. *Digestion* 2011;83:46-53.
233. Cremonini F, Houghton L, Camilleri M, et al. Barostat testing of rectal sensation and compliance in humans: comparison of results across two centres and overall reproducibility. *Neurogastroenterol Motil* 2005;17:810-820.
234. Vanhoutvin SA, Troost FJ, Lindsey P, et al. Alternative procedure to shorten rectal barostat procedure for the assessment of rectal compliance and visceral perception: a feasibility study. *J Gastroenterol* 2012;47:896-903.
235. Sauter M, Heinrich H, Fox M, et al. Toward more accurate measurements of anorectal motor and sensory function in routine clinical practice: validation of high-resolution anorectal manometry and rapid barostat bag measurements of rectal function. *Neurogastroenterol Motil* 2014;26:685-695.

FIGURE LEGENDS

Figure 1. Schematic drawing demonstrating the symptom-based spectrum of functional constipation (FC) and irritable bowel syndrome with constipation (IBS-C), and biomarkers that may be used to discriminate these conditions from each other. From Whitehead et al 2016.⁴³

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Figure 2. Schematic drawing highlighting the multifactorial pathophysiological mechanisms common to coexistent faecal incontinence (FI) and chronic constipation (CC).^{65,67,70,73}

Figure 3. Schematic of principal (overlapping) pathophysiological mechanisms in chronic constipation.

Figure 4. Representative example of a meal response in the descending and sigmoid colon of a healthy adult (A) and a patient with STC (B). In the top two images (A and B), the entire recording is shown 2 h prior to and after the meal. A rapid increase in colonic activity can be seen in the healthy subject after the meal is given (Blue line); this response is not evident in the patient. In (C) and (D), an expanded section of the meal response is shown from the area inside the red-hatched boxes in the top two images. In (C), the retrograde cyclic motor pattern is evident (purple arrow). In the expanded section of the patient trace (D) 2–3 cpm activity can be seen, but the cyclic propagating motor pattern is not evident. In this section of the trace, two retrograde short single motor pattern can be seen (purple arrows). The spatiotemporal pressure plots of (C) and (D) are shown in (E) and (F). The purple arrows in (C) and (D) are shown as white arrows in the bottom two images. From Dinning et al, 2015.¹²³

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Figure 5. Rectal pressure-volume relationships determined through use of the electromechanical barostat (phasic isobaric distension protocol) in constipated patients with rectal hyposensitivity (RH) to balloon distension, constipated patients with normal rectal sensation (NS), and healthy volunteers (HV). Both rectal capacity (reflected by elevated distension volumes) and rectal compliance (steeper slope of the linear section of the curve) are increased in patients with RH. Adapted from Gladman et al.²²⁸

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Figure 6. Examples of both a screening method (A: plain abdominal X-ray following previous ingestion of radio-opaque markers) and more advanced method (B: full Wireless Motility Capsule study) for the diagnostic assessment of whole-gut transit. The X-ray shows retention of all 60 ingested markers (Metcalf method:¹⁹¹ 3 different marker sets) at 120 hr, clearly demonstrating a pathological delay in whole-gut transit ($\geq 20\%$ of markers remaining). The Wireless Motility Capsule study (different patient) shows temperature (blue trace), pH

(green trace) and pressure (red trace) changes throughout the study period. Using stereotypical alterations in the pH profile (abrupt rise [white arrow] – stomach to small bowel transition, and sharp drop [yellow arrow] – small to large bowel transition), regional GI transit can be determined. This recording shows normal gastric emptying (3 hr 55 min; upper limit of normal: 5 hr¹⁸⁸), but a pathological delay in transit through both the small bowel (13 hr 3 min; upper limit of normal: 8 hr¹⁸⁸) and colon (85 hr 45 min; upper limit of normal: 50 hr 30 min¹⁸⁸). Whole-gut transit time (from ingestion, left border of recording to expulsion, left border of recording) is also delayed (102 hr 44 min; upper limit of normal: 68 hr 45 min¹⁸⁸).